Chapter 79

White Matter, Schizophrenia, and Cannabis

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Abbreviations

2-AG 2-Arachidonoylglycerol
AK Axial kurtosis
CB1R Cannabinoid receptor-1
CB2R Cannabinoid receptor-2
CNPase 2′,3′-Cyclic nucleotide 3′-phosphodiesterase
DTI Diffusion tensor imaging
FA Fractional anisotropy
MAG Myelin-associated glycoprotein
MBP Myelin basic protein
MD Mean diffusivity
RD Radial diffusivity
SLF Superior longitudinal fasciculus
TBSS Tract-based spatial statistics
THC Tetrahydrocannabinol
WM White matter

INTRODUCTION

Schizophrenia can be a chronic severe disorder that has an estimated prevalence worldwide of 0.5–1.0% and an average age of onset in late adolescence and young adulthood. Much investigation has been done to try to carefully identify pathological changes that suggest possible biological mechanisms underlying the disease; however, the definitive causes of schizophrenia are currently not fully known. One of the most reproducible neurobiological abnormalities reported in schizophrenia is structural dysconnectivity, seen functionally as cognitive deficits and structurally as abnormalities in brain white matter (WM). Multiple lines of evidence have indicated that cannabis use, in particular during the important phase of adolescent brain development, may be a risk factor for the development of schizophrenia in those individuals sensitive to a gene×environment interaction. The focus of this chapter is on reviewing the evidence for WM changes in schizophrenia in relation to cannabis use.

The human brain is composed of two main neuronal tissue types—WM and gray matter. WM, so-called for its pale appearance in fixed postmortem tissue, comprises the main fiber tracts within the brain. The white color derives from the lipid content of the myelin wrapping of the fiber bundles, which provides insulation similar to the plastic coating on copper wiring and speeds conductance of nerve impulses along the fiber tracts. Myelin is produced by oligodendrocytes, a type of neuroglial cell that extends many processes, which repeatedly wrap an axon, forming this multilayer membrane of myelin (Baumann & Pham-Dinh, 2001). WM is predominantly a tissue involved in efficiently conducting nerve impulses throughout the brain.

WM can be grouped into three main classes of tracts. The first are projection fibers. These tracts are generally arranged vertically, allowing signals to be passed from lower brain regions (and the spinal cord) to higher ones and vice versa. The corticobulbar tract joins projections from many areas of the cortex to the brainstem. The corticospinal tract projects from the pre- and postcentral gyri and travels to the pyramidal tract at the pons. All thalamic radiations converge into the internal capsule, located between the putamen and the thalamus–caudate nucleus regions. The corticobulbar and corticospinal tracts and the thalamic fibers all penetrate the internal capsule, where the cortex–brainstem connection occupies the more lateral regions. The second group of fibers are the association fibers. These are intrahemispheric fiber pathways connecting either different lobes of that hemisphere (long association fibers) or signals from one gyrus to the next (short association fibers). The four best characterized association tracts are the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus. The third and final group of fibers are the commissural or callosal fibers. These fibers connect the two hemispheres of the brain from the various gyri and nuclei within a single cerebral hemisphere to corresponding locations in the opposite hemisphere. The best known is the massive array of projections across the corpus callosum that forms the so-called callosal radiation. The projections from the genu of the corpus callosum form the forceps minor; those from the splenium form the forceps major. There are also strong projections from the splenium that sweep inferiorly along the lateral margin of the posterior horn of the lateral ventricle and project into the temporal lobes; these projections are known collectively as the tapetum. See Figure 1 for an illustration.

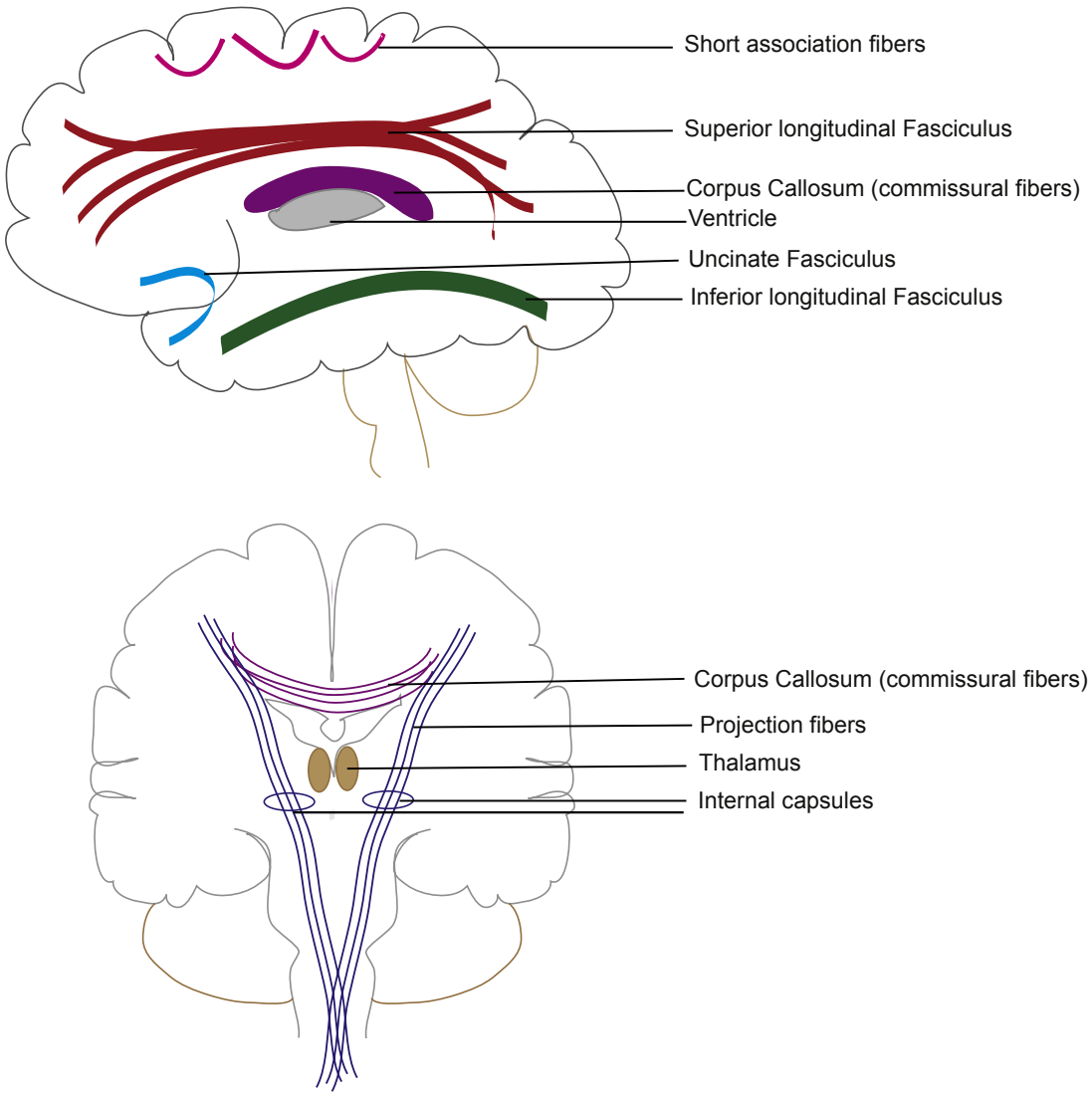

FIGURE 1 Diagram of the major WM tracts in the human brain. Cartoon of the location of various association, projection, and commissural WM tracts in the human brain seen in both a sagittal (top) and a coronal (bottom) view.

White Matter and the Endocannabinoid System

An interesting and important point in this discussion is that WM contains receptors for cannabis. *Cannabis sativa* (cannabis) contains greater than 70 different cannabinoid compounds, with Δ^9-tetrahydrocannabinol (THC) being the best characterized. The psychoactive properties of THC are the result of an interaction of THC with the body's endogenous cannabinoid system. The endogenous endocannabinoid ligands, 2-arachidonoylglycerol and anandamide being the two best characterized, activate receptors that are involved in intercellular communication and intracellular metabolism. This system is used by the human body for a variety of functions, including cognitive, emotional, and pain processing. Additionally, the endocannabinoid system is involved in brain development and maturation, in particular axon guidance and growth, and neuroplasticity. We currently know of two G-protein-coupled receptors, cannabinoid receptor-1 (CB1 receptor) and cannabinoid receptor-2 (CB2 receptor), that interact with these endogenous ligands. CB2 receptors are predominantly expressed on cells of the immune system. The CB1 receptor is 68% homologous to the CB2 receptor, but in contrast is found predominantly on cells of the peripheral and central nervous system. CB1 receptors are found in a particularly high concentration in dopamine receptor-rich areas of the brain, such as the hippocampus and basal ganglia, and expressed on nervous system tissues from the early embryonic period onward. Interestingly, there are temporal and regional variations of CB1 receptor distribution from the fetal period to adulthood, with greater WM expression during the fetal period that slowly changes to a greater receptor density in gray matter in adulthood (Chadwick, Miller, & Hurd, 2013).

The endocannabinoid system is active during adolescence, so it is important to appreciate the potential effects of cannabis use on the adolescent developing brain. In normal brain development and maturation, after a burst of synapse building in the preadolescent period, synaptic density decreases by 40% in adolescents (between the ages of 7 and 15), demonstrating that active synaptic remodeling is taking place during this phase of development.

Brain regions such as the hippocampus and frontal cortex are continuing to develop and mature during this period and levels of endocannabinoids are increased in these brain regions during adolescence compared to adulthood. Significant levels of endocannabinoid receptors have also been found in WM tracts of the adolescent brain, for example, on the glial cells responsible for the production and maintenance of WM (e.g., astrocytes and oligodendrocytes). As with the endocannabinoids, the distribution of CB1 receptors is not in its adult configuration until the end of adolescence, a significant difference between adult and adolescent brain (Chadwick et al., 2013). Thus adolescence represents a period of heightened CB1 receptor density and possibly functionality, meaning that the effects of cannabis during this time could be fundamentally different from the effects on a mature brain. It has therefore been postulated that early adolescent cannabis exposure interacts with the endocannabinoid processes, adversely affecting the trajectory of WM development, ultimately triggering psychosis in individuals who are vulnerable to the illness (Bava et al., 2009).

Measurement of White Matter Structural Connectivity

Structural connectivity refers to neuroanatomy that can be seen or measured at a macroscopic level by magnetic resonance imaging and microscopically by staining of postmortem tissue. In vivo structural connectivity of WM can be measured by diffusion tensor imaging (DTI). This magnetic resonance imaging technique uses a series of gradient pulses that are measured in multiple directions at once, typically 25 to 55. This allows the detection of diffusion of water molecules. Diffusion that is restricted to a particular direction is referred to as being anisotropic (such as is seen in axons) and the measure of freely moving water is referred to as isotropic (as is seen in ventricles). The amount of anisotropy in a measured region is quantified as the fractional anisotropy, or FA, and is a value between 0 (isotropic) and 1 (highly restricted). Another common measure is mean diffusivity, or MD, and it reflects the magnitude of the water movement but without directionality. Tractography can also be performed on the DT images, which can illustrate and examine the connections between regions of interest. The comparison of tracts between individuals is commonly done using tract-based spatial statistics (TBSS). WM can also be quantified by measuring the volume of WM tissue using voxel-based morphometry. Overall, DTI allows for characterization of WM in living individuals (see Figure 2 for illustration).

WM can also be studied in postmortem tissue. Postmortem investigations can be completed with either light or electron microscopy to look for abnormalities of the myelin sheath surrounding axons and of the oligodendrocytes that produce the myelin sheath. The study of WM in postmortem tissue by either method involves staining of the tissue for WM- or oligodendrocyte-associated proteins such as myelin basic protein (MBP), myelin-associated glycoprotein (MAG), and 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase). Each of these proteins has a particular profile in the healthy brain. MBP is found only in mature oligodendrocytes and is involved in the process of compacting myelin (see Figure 3 for an example of MBP staining) (Baumann & Pham-Dinh, 2001). MAG is found in the periaxonal membrane of the mature oligodendrocyte.

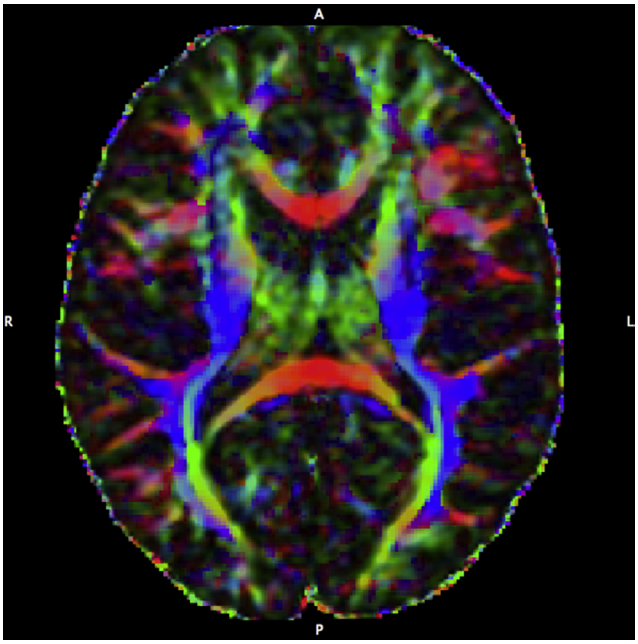

FIGURE 2 Diffusion tensor FA map. Human DT image showing prominent diffusion tensor direction by FA mapping. DTI was performed on a healthy subject at a field strength of 1.5T with 3-mm-thick slices (General Electric Healthcare, Fairfield, CT, USA). FA mapping was done using FMRIB's Diffusion Toolbox (Functional MRI of the Brain, FMRIB Analysis Group, Oxford, UK). The color convention is as follows: red for fibers crossing from left to right, green for fibers traversing in the anteroposterior direction, and blue for fibers going from superior to inferior portions of the brain.

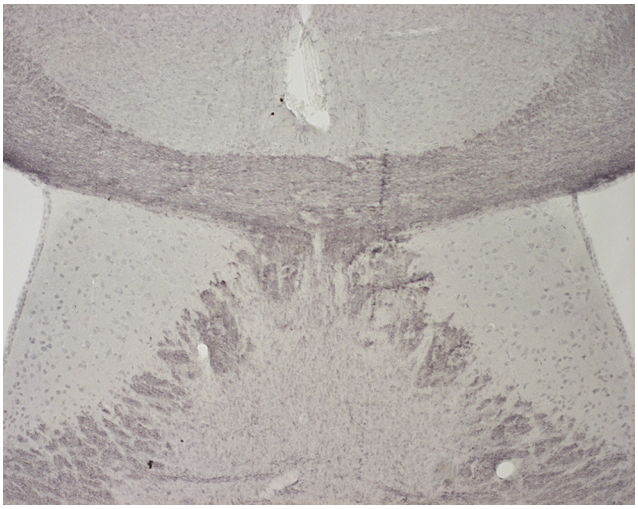

FIGURE 3 Myelin staining. Murine cerebral cortex tissue stained MBP by immunohistochemistry (formalin/paraformaldehyde-fixed section). Samples were blocked with 2.5% serum for 1 h followed by incubation with the primary antibody at a 1/200 dilution for 18 h. A biotin-conjugated rabbit anti-rat polyclonal antibody was used as the secondary antibody at a 1/500 dilution.

CNPase has a different distribution; it is absent from compacted myelin and instead is found in oligodendrocyte cytoplasm. CNPase can be detected early in development and at several stages of cell maturation in the precursor cells to oligodendrocytes (Baumann & Pham-Dinh, 2001).

WHITE MATTER CHANGES IN SCHIZOPHRENIA

Dysconnectivity is the most common abnormality reported in schizophrenia. While there is debate about whether this observation is a primary factor in causing schizophrenia or the result of other cortical dysfunction is not clear at this time. However, the end result is failed or at least inadequate information transfer between neurons and brain regions in affected individuals. There is a large body of literature examining WM in chronic schizophrenia patients, which is complicated by the "chicken or egg"-type discussion, that is, do WM abnormalities lead to schizophrenia or does schizophrenia affect WM structure itself? Most studies use a voxel-based morphometry or TBSS approach; however, there is variability among the studies, including replication difficulties, accounted for in part by lack of systematic control for specific variables such as correction for age and medication (Fitzsimmons, Kubicki, & Shenton, 2013). Age is an important consideration as WM integrity and oligodendrocyte apoptosis vary with age, especially during the adolescent years (Engelter, Provenzale, Petrella, DeLong, & MacFall, 2000; Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010).

Findings of reduced FA in schizophrenia have been reported for the internal capsule, the anterior thalamic radiation, the left inferior longitudinal fasciculus, the left inferior frontal-occipital fasciculus, and portions of the uncinate fasciculus (Kubicki & Shenton, 2014). There are a number of DTI studies that extend the finding of decreased FA and correlate decreases in WM with negative symptom severity (Bracht et al., 2014). An argument for damage to WM resulting in the development of schizophrenia arises from DTI studies that include individuals with first-episode psychosis. These firmly establish that WM abnormalities exist before medication treatment begins and at the very early stages of illness (Andreasen et al., 2011; Kubicki & Shenton, 2014; Zhang et al., 2014). Even more evidence for causation versus epiphenomenon comes from work examining individuals who are currently healthy but who have childhood and adolescent risk factors for psychosis. These individuals show decreased FA values in the superior longitudinal fasciculus, which suggests further weight to the "two-hit" hypothesis of schizophrenia development (DeRosse et al., 2014). This hypothesis suggests that it takes both a genetic predisposition (the so-called first hit) and a second environmental or sociological insult (the second hit), such as cannabis use, to enable the development of schizophrenia (Figure 4) (Bayer, Falkai, & Maier, 1999).

Another method of more closely examining the cell packing of WM is diffusion kurtosis imaging (DKI). DKI has exhibited improved sensitivity and specificity in detecting developmental and pathological changes in neural tissues compared to conventional DTI. Zhu et al. (2015) examined by DKI the corpus callosum and internal capsule of chronic schizophrenia patients. They found significant abnormalities in two measures, axial kurtosis (AK) and radial diffusivity (RD). In schizophrenia patients, a measurement of decreased AK suggests axonal damage; however, the increased RD indicates myelin impairment. These findings suggest that diffusion and kurtosis parameters could provide complementary information and they should be jointly used to further elucidate pathological changes in schizophrenia (Zhu et al., 2015).

Postmortem studies also illustrate WM abnormalities in schizophrenia. Again, this work has not always been replicated. A possible reason for this inconsistency in both the neuroimaging and the postmortem work is the possible heterogeneity of the schizophrenic patient population used, and there is some evidence of antipsychotic drugs affecting WM (Ozcelik-Eroglu et al., 2014). With this caution in mind, there is postmortem evidence of increased cell density in deep WM along with maldistribution of neurons in deeper WM prefrontal cortex (Akbarian et al., 1996). There is also evidence of problems with myelin sheath formation, increased numbers of abnormal fibers, and oligodendroglial cell ultrastructure (Uranova, Vikhreva, Rachmanova, & Orlovskaya, 2011). Reductions in deep-WM, but not gyral, myelin staining have been seen with light microscopy in postmortem tissue from patients with schizophrenia compared to healthy controls, but the results were not statistically significant (Regenold et al., 2007). Another avenue of postmortem exploration relevant to our discussion here is a study that examined the cytoarchitecture of the substantia nigra by examining dopaminergic neurons, cells that are affected directly by THC. In this 2014 study, astrocyte density was decreased, but not oligodendrocyte density, in this region in schizophrenic patients compared to healthy controls and another patient group affected by depression (Williams et al., 2014). It has also been reported that cross-sectional WM decreases were more significant in the left superior gyrus of older (65–84 years) patients compared to younger (30–54 years) patients and age-matched healthy controls (Torii et al., 2012). This is in agreement with a longitudinal imaging study showing progressive losses in frontal lobe WM volume seen over a 3-year period, and these losses correlated with negative symptoms (Ho et al., 2003). However, what is not known is if significant WM changes early in the illness result in even more negative changes over the life span.

WHITE MATTER CHANGES WITH CANNABIS USE

Cannabis is generally considered not to be neurotoxic, so one might expect not to find differences in WM between users and nonusers. However, this assumption of lack of neurotoxicity is based primarily on animal studies of cannabis use and there are several reasons this may not be valid in humans. First, there is significant molecular divergence between the sequences for the CB1 receptor in rodents and humans (McPartland, Matias, Di Marzo, & Glass, 2006). Second, the receptor affinity for THC is significantly different between the species, and third, the distribution of CB1 receptors is different, with denser CB1 receptor expression in cognitive regions such as cerebral cortex in humans compared with rats (McPartland, Glass, & Pertwee, 2007). The assumption of cannabis being harmless based on animal research is therefore suspect; the animal work cannot be translated directly to humans. Hence, it is not surprising that all papers in this small body of literature show damage to WM in cannabis users. We considered all papers with greater than 10 subjects to allow for a sufficient breadth of literature to discuss here (see Table 1).

DTI studies show deficits in WM structural integrity with cannabis use in comparison to nonusing control subjects. Most of the studies examining DTI in cannabis users had a subject population that was either adolescent or young adult. Heavy cannabis use was associated with damage to the corpus callosum that is reflected in an increased MD value (Arnone et al., 2008). Damage with heavy

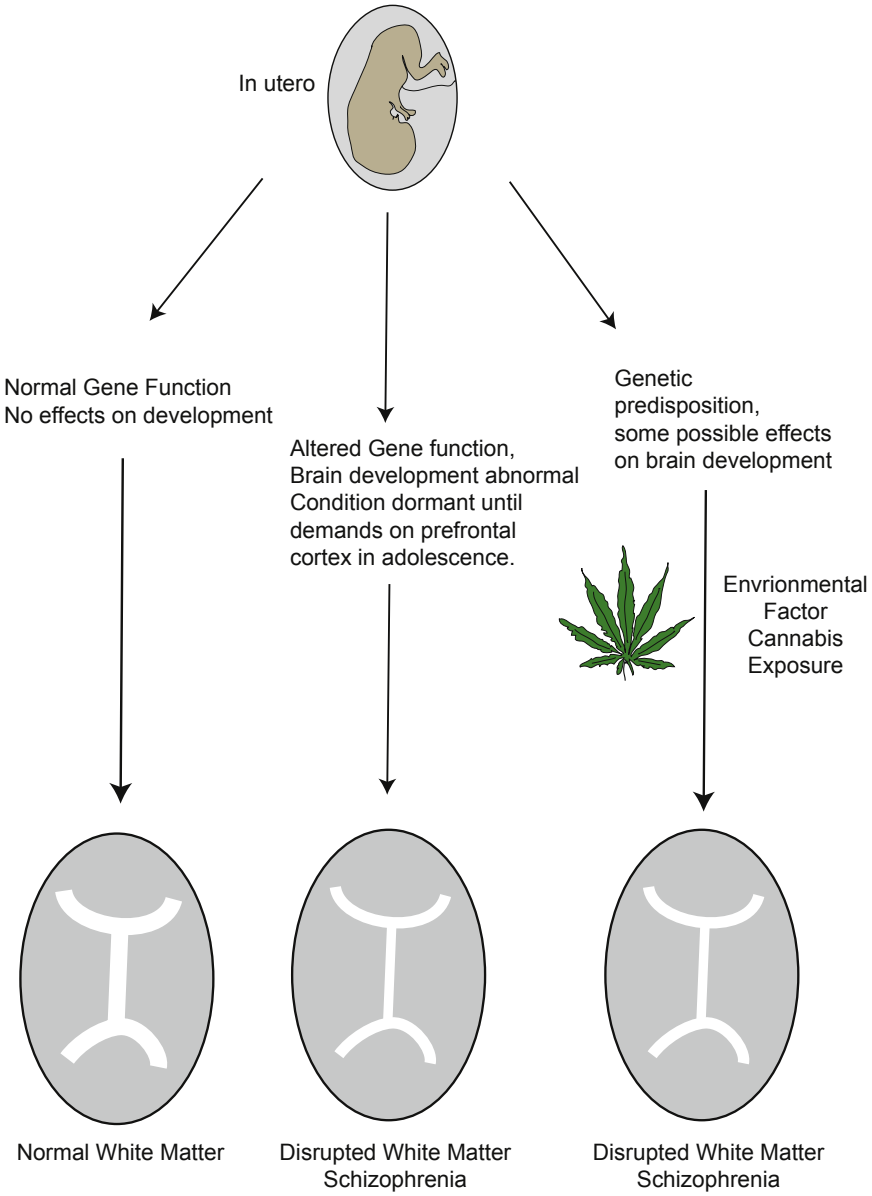

FIGURE 4 Illustration of two possible models of WM disruption leading to the development of schizophrenia. The two most common models of schizophrenia development are the genetic and the two-hit hypotheses. Here we show a modeling of the genetic and the two-hit hypotheses leading to disruptions in WM development, disorganization, and reduced myelination in a timeline fashion from conception to disease onset.

use was also noted to the frontotemporal region and the superior longitudinal fasciculus (SLF) as measured by tractography and with decreased FA values (Ashtari et al., 2009). Another group confirmed these findings in the SLF and found decreased FA in the hippocampus as well (Yucel et al., 2010). Decreased FA in the SLF was a definitive finding in two other studies that examined a variety of substance-use-dependent subjects with a cannabis subanalysis (Bava et al., 2009; Clark, Chung, Thatcher, Pajtek, & Long, 2012). Decreased FA was also measured in regions of the corpus callosum and the internal capsule in users in another study of cannabis-using adults (Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014). What is interesting about this study is a subanalysis that showed that individuals who began cannabis smoking prior to age 16 had greater decrements in FA than those who began after age 16 (Gruber et al., 2014). This again is supportive of age of cannabis use onset effects on WM development, which parallels the epidemiological studies reporting age of regular use effects on risk of psychosis development.

Measurements of FA and MD both suggest changes in axonal connections and integrity of fiber tracts with cannabis use in an otherwise healthy population. Tractography and mapping of nerve cell connections are other methods to investigate WM changes. Synaptic remodeling, as measured by axonal connectivity analyses (by diffusion-weighted magnetic resonance imaging and mapping), was impaired in a measurable way in cannabis users compared to nonusers, in the right fimbria, the commissural fibers, and the corpus callosum, structures that contain abundant levels of cannabinoid receptors in the developing brain (Zalesky et al.,

TABLE 1 Diffusion Tensor Imaging Studies of White Matter with Cannabis Use

First Author (year)	Group (n)	Age, Years, Mean (SD)	Controlled for Comorbid Alcohol Use	Controlled for Other Illicit Substances	Results
Clark et al. (2012)	CAN+ (31) HC (20)	17 (1) 16 (1)	No	Group of 31 a subset of other substance use disorders	CAN+<HC in FA in SLF. Significant gender effect.
Kim et al. (2011)	CAN+ (12) HC (13)	19 (1) 22 (4)	Excluded more than 21 drinks per week in the past month or more than 5 drinks per occasion	No other illicit drugs previous 3 months	Decreased regional connectivity in CAN+. Tractography showed global network decreases in efficiency and altered regional connectivity.
Gruber et al. (2014)	CAN+ (25) HC (18)	23 (6) 23 (4)	Groups matched for alcohol consumption	Exclusion of other illicit drugs	CAN+<HC in FA. Subanalysis with earlier start (14 vs 17 years) showed greater FA decrease.
Zalesky et al. (2012)	CAN+ (59) HC (33)	33 (11) 32 (12)	Groups matched for alcohol consumption	Exclusion of other illicit drugs	CAN+<HC in FA, axonal connectivity reduced in callosal and limbic fiber tract families.
Ashtari et al. (2009)	CAN+ (14) HC (14)	19 (1) 19 (1)	5 CAN+ had concurrent alcohol abuse	Exclusion of other illicit drugs	CAN+<HC in FA, axonal connections increased in frontotemporal area.
Arnone et al. (2008)	CAN+ (11) HC (11)	25 (3) 23 (3)	Excluded more than 21 drinks per week in the past month	No other illicit drugs previous 6 months	No differences in FA in the corpus callosum. MD significantly increased in corpus callosum between prefrontal lobes.
Yucel et al. (2010)	CAN+ (11) HC (8)	19 (2) 20 (3)	No	Excluded if inhalants were used for 6 months or more.	CAN+<HC in FA in both hippocampi and right SLF.
Bava et al. (2009)	CAN+ (36) HC (36)	18 (1) 18 (1)	Subjects used both alcohol and cannabis	Excluded use of psychoactive drugs	CAN+<HC in FA in left SLF, left postcentral gyrus, and inferior frontotemporal tracts.
Clark et al. (2012)	CAN+ (31) HC (20)	17 (1) 16 (1)	Alcohol use significantly different between control and substance use group	None	CAN+<HC in FA in prefrontal and parietal volumes.

The minimal threshold for significance is $p<0.05$ (uncorrected for comparisons); HC, healthy control; CAN+, cannabis using; FA, fractional anisotropy; MD, mean diffusivity; SLF, superior longitudinal fasiciculus.

2012). Another method of examining axonal connectivity is to use a graph theoretical model in conjunction with DTI. This method showed that brain networks in cannabis-using subjects were significantly less integrated and have altered regional connectivity, for example, in the cingulate region, compared to healthy nonusing controls (Kim et al., 2011). There is one other 2014 study to mention, even though it does not use DTI, that suggests even irregular cannabis use may be detrimental to the human brain. This study used magnetic resonance imaging to examine the size, shape, and density of the nucleus accumbens and the amygdala in 20 cannabis-using adolescents and 20 nonusers. Larger abnormalities in both brain structures were associated with greater cannabis intake (Gilman et al., 2014). All of these studies show that WM connectivity and integrity are reduced with cannabis use in an otherwise healthy population.

WHITE MATTER CHANGES WITH CANNABIS USE IN PEOPLE WITH SCHIZOPHRENIA

There is very little literature on the combined influences of cannabis consumption and schizophrenia on WM structure (see Table 2). This is a field of research that would benefit from longitudinal studies on this population. A discussion of cannabis use in schizophrenia is important; as previously mentioned, there is strong epidemiological evidence of a link between adolescent cannabis use and the development of schizophrenia (Andreasson, Allebeck, Engstrom, & Rydberg, 1987; Burns, 2013). The effect of cannabis on WM is one possible mechanism by which cannabis may promote the development of psychosis. The few DTI studies done as of this writing have limited conclusions owing to the inclusion of comorbid drug and alcohol use, and there are conflicting results from these studies. An intriguing finding from one of these studies suggests that cannabis use prior to age 17 creates a subgroup of patients with hyperconnectivity. This is counter to the majority of DTI research into schizophrenia, which shows decreased FA and hypoconnectivity. This study showed increased FA in the left posterior corpus callosum and right occipital and left temporal lobes in cannabis-using patients compared to healthy controls but no significant difference from cannabis-naïve patients (Peters et al., 2009). However, these same patient populations had a significant increase in FA values due to hard drug use as well, a significant confound to any conclusion about what the source of increased connectivity might be (Peters et al., 2009). James et al. (2011), showed decreased FA in cannabis-using schizophrenia patients in brainstem, internal capsule, corona radiata, and superior and inferior longitudinal fasciculus. However, another study using TBSS performed on using and nonusing first-episode psychosis patients showed no difference in WM parameters (Haller et al., 2013). This study is notable for its prospective design; however, no healthy control users or nonusers were included, making the

TABLE 2 Diffusion Tensor Imaging Studies of White Matter with Cannabis and Schizophrenia

First Author, Year of Publication	Group (n)	Age, Years, Mean (SD)	Controlled for Comorbid Alcohol Abuse	Controlled for Comorbid Stimulant Use	Results
Peters et al. (2009)	FEP CAN+ (35) HC (21)	22 (4) 23 (3)	Excluded alcohol abuse or dependence in HC	Exclusion of other illicit drugs in HC	FEP with cannabis use prior to age 17 had increased FA in bilateral uncinate fasciculus, anterior internal capsule, and frontal WM. FA highest in CAN+ FEP+ subgroup with history of other illicit drug use.
Epstein et al. (2014)	FEP (53) UHR (19) CAN+ (28) HC (53)	17 (2) 16 (3) 18 (2) 17 (3)	No	Exclusion of other illicit drugs	Corticospinal and left ILF and left inferior fronto-occipital FAs were all significantly different between FEP and controls. Left ILF in CAN+ had significantly decreased FA relative to HC. Corticospinal significantly different between CAN+ and FEP. 21 of the 55 FEP had cannabis use disorder diagnosis
Haller et al. (2013)	FEP CAN+ (33) FEP CAN– (17)	23 (4) 24 (4)	No	Exclusion of other illicit drugs	No difference between CAN– and CAN+ SCZ.
James et al. (2011)	FEP (32) CAN+ SCZ (16) CAN– SCZ (16) HC (28)	16 (1) 16 (1)	No heavy alcohol use reported by subjects	Exclusion of other illicit drugs	FEP<controls in FA, in association, brainstem, callosal and projection fibers. CAN+ FEP<CAN– FEP in FA, in brainstem, projection, and association fiber tracts

The minimal threshold for significance is $p<0.05$ (uncorrected for comparisons). FEP, first-episode psychosis; HC, healthy control; UHR, high risk for psychosis; SCZ, schizophrenia; CAN+, cannabis using; CAN–, not cannabis using; FA, fractional anisotropy; ILF, inferior longitudinal fasciculus.

impact of disease impossible to gauge (Haller et al., 2013). There is one other paper that examined schizophrenia and cannabis use in the same study but not in a separate group of cannabis-using schizophrenia subjects. Epstein et al. found decreased FA in cannabis users relative to healthy controls in the left inferior longitudinal fasciculus and the corticospinal tracts. First-episode psychosis patients studied in the same manner showed lower FA values in the corticospinal tracts than both the cannabis users and the healthy controls (Epstein et al., 2014). Twenty-one of the fifty-five psychosis subjects had cannabis use histories, but only eight had a positive urinalysis during the study (Epstein et al., 2014).

No postmortem papers on the state of WM in cannabis-using schizophrenia patients were found. However, some postmortem work has been done on cannabinoid receptor expression. CB1 receptors were reported to be downregulated in human brain with chronic use (Villares, 2007). Binding experiments in cannabis-using schizophrenia patients showed increased binding to CB1 receptors in the prefrontal cortex that was independent of recent cannabis consumption compared to cannabis-using controls (Dean, Sundram, Bradbury, Scarr, & Copolov, 2001). This absence of downregulation in schizophrenia could be another piece of the cannabis and schizophrenia puzzle.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

Cannabis is not the only recreational substance to affect WM integrity. This is one of the major confounders to cannabis research, as there are very few users that are purely cannabis using. In other words, cannabis use is frequently comorbid with other drug use (Tsuang et al., 1998). Published studies presented here struggled particularly with exclusion of alcohol use. There are some studies that examine alcohol and cannabis use together. One study examined eight different WM regions in binge-drinking adolescents with or without cannabis use and healthy controls. This study showed significant differences in FA in all eight WM regions between the binge-drink-only group and controls, including the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and SLF (Jacobus et al., 2009). Similar to one of the schizophrenia and cannabis papers, in four of these same regions, binge drinkers who were also heavy cannabis users had higher FA than nonusing binge drinkers (Jacobus et al., 2009; Peters et al., 2009). A prospective follow-up DTI study done by the same group on 16 adolescents (ages 16–18 years) with minimal alcohol and marijuana use who were scanned again 3 years later showed FA decreased in those individuals who initiated heavy alcohol and cannabis use but not for alcohol use alone (Jacobus, Squeglia, Infante, Bava, & Tapert, 2013). Another paper cited in the cannabis section examined cannabis users, inhalant users, and healthy controls and found lower FA values for both user groups but greater decreases in the inhalant group (Yucel et al., 2010). Another study showed WM disorganization of the SLF in all substance-dependent individuals, but the examination of specific substance-related variables to changes in the prefrontal cortex and parietal lobe FA showed a strong association with cannabis-related symptoms but not alcohol-related symptoms (Clark et al., 2012). The SLF, in addition to the inferior frontal and temporal lobe WM tracts, was also noted to have decreased FA in alcohol and marijuana users in another study comparing 36 users to 36 demographically similar healthy control subjects (Bava et al., 2009). Reduced FA has also been reported in the frontal lobe with cocaine use (Lim, Choi, Pomara, Wolkin, & Rotrosen, 2002). To further understand the effects of cannabis on WM structure and function, future studies thus have to take into consideration, and control for, the comorbidity of other substances of abuse.

DEFINITION OF TERMS

Schizophrenia This is a chronic long-term mental disorder that causes people to interpret reality abnormally. Schizophrenia is characterized as having core symptom clusters of positive, such as hallucinations, and negative symptoms, such as loss of personality, and cognitive deficits such as working memory abnormalities.

Early phase psychosis The first time someone experiences psychotic symptoms or a psychotic episode and the subsequent critical 2–5 years of illness are known as the early phase.

White matter This is a component of the central nervous system that is mostly composed of glial cells and myelinated axons. This tissue is pale in color and when formalin-fixed appears white.

White matter tracts These are bundles of myelinated nerve axons. The tracts form groups of known WM fibers called projection, association, and commissural tracts in the cerebral hemispheres.

Gray matter This is the other major component of the central nervous system, primarily composed of nerve cell bodies, unmyelinated axons, astroglia, and branching dendrites. This tissue appears darker in color than WM.

Diffusion tensor imaging This is the magnetic resonance spectroscopy method for characterizing neuropathology by measuring the movement of water within the brain.

Fractional anisotropy This is the amount of anisotropy measured in a region by DTI and quantified as a directional value between 0 (isotropic) and 1 (highly restricted).

Mean diffusivity This is the magnitude of the water movement measured by DTI but without directionality.

Myelin This is a mixture of proteins and phospholipids formed by oligodendrocytes that create an insulating sheath around many nerve fibers.

Oligodendrocyte This is a type of neuroglia that wraps axons and produces myelin.

KEY FACTS

Key Facts about White Matter in Schizophrenia

- WM abnormalities exist at disease onset.
- WM abnormalities may be the result of life experiences, such as cannabis use, that are risk factors for developing psychosis.
- There are genes affecting WM development that are associated with schizophrenia.
- WM loss may be accelerated with aging in people with schizophrenia.
- Greater WM deficits are associated with worse negative symptoms and cognitive problems.

Key Facts about the Association between White Matter, Adolescent Cannabis Use, and Schizophrenia

- The endocannabinoid system is important for brain development and maturation, particularly during adolescence.
- There is a temporal pattern associated with CB1 receptor and endocannabinoid ligands—higher expression during adolescence than adulthood.
- Adolescent use of cannabis is associated with higher risk of schizophrenia development as seen in large epidemiologic studies.
- Cannabis can affect the trajectory of WM development in an otherwise healthy population.
- Cannabis plus genetic liability can alter the trajectory of WM development toward the development of psychosis.

SUMMARY POINTS

- WM is a type of brain tissue that speeds conductance of electrical signals through the body.
- Changes in WM can be measured in vivo by DTI and in vitro by postmortem staining.
- Studies of WM brain tissue in patients with schizophrenia show agreement when the studies are corrected for age and other comorbidities.
- Studies of WM in cannabis users are in good agreement that WM integrity is damaged with chronic and heavy use and possibly also with recreational use.
- Studies of WM in cannabis-using people with schizophrenia are lacking as the studies that have been done are all complicated by lack of healthy control subjects or lack of controls for other substance use.

REFERENCES

Akbarian, S., Kim, J. J., Potkin, S. G., Hetrick, W. P., Bunney, W. E., Jr., & Jones, E. G. (1996). Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. *Archives of General Psychiatry*, *53*(5), 425–436.

Andreasen, N. C., Nopoulos, P., Magnotta, V., Pierson, R., Ziebell, S., & Ho, B. C. (2011). Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. *Biological Psychiatry*, *70*(7), 672–679. http://dx.doi.org/10.1016/j.biopsych.2011.05.017. pii:S0006-3223(11)00546-4.

Andreasson, S., Allebeck, P., Engstrom, A., & Rydberg, U. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet*, *2*(8574), 1483–1486.

Arnone, D., Barrick, T. R., Chengappa, S., Mackay, C. E., Clark, C. A., & Abou-Saleh, M. T. (2008). Corpus callosum damage in heavy marijuana use: preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. *NeuroImage*, *41*(3), 1067–1074. http://dx.doi.org/10.1016/j.neuroimage.2008.02.064.

Ashtari, M., Cervellione, K., Cottone, J., Ardekani, B. A., Sevy, S., & Kumra, S. (2009). Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. *Journal of Psychiatric Research*, *43*(3), 189–204. http://dx.doi.org/10.1016/j.jpsychires.2008.12.002.

Baumann, N., & Pham-Dinh, D. (2001). Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiological Reviews*, *81*(2), 871–927.

Bava, S., Frank, L. R., McQueeny, T., Schweinsburg, B. C., Schweinsburg, A. D., & Tapert, S. F. (2009). Altered white matter microstructure in adolescent substance users. *Psychiatry Research*, *173*(3), 228–237. http://dx.doi.org/10.1016/j.pscychresns.2009.04.005.

Bayer, T. A., Falkai, P., & Maier, W. (1999). Genetic and non-genetic vulnerability factors in schizophrenia: the basis of the "two hit hypothesis". *Journal of Psychiatric Research*, *33*(6), 543–548.

Bracht, T., Horn, H., Strik, W., Federspiel, A., Razavi, N., Stegmayer, K., … Walther, S. (2014). White matter pathway organization of the reward system is related to positive and negative symptoms in schizophrenia. *Schizophrenia Research*, *153*(1–3), 136–142. http://dx.doi.org/10.1016/j.schres.2014.01.015.

Burns, J. K. (2013). Pathways from cannabis to psychosis: a review of the evidence. *Front Psychiatry*, *4*, 128. http://dx.doi.org/10.3389/fpsyt.2013.00128.

Chadwick, B., Miller, M. L., & Hurd, Y. L. (2013). Cannabis use during adolescent development: susceptibility to psychiatric illness. *Front Psychiatry*, *4*, 129. http://dx.doi.org/10.3389/fpsyt.2013.00129.

Clark, D. B., Chung, T., Thatcher, D. L., Pajtek, S., & Long, E. C. (2012). Psychological dysregulation, white matter disorganization and substance use disorders in adolescence. *Addiction*, *107*(1), 206–214. http://dx.doi.org/10.1111/j.1360-0443.2011.03566.x.

Dean, B., Sundram, S., Bradbury, R., Scarr, E., & Copolov, D. (2001). Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience*, *103*(1), 9–15.

DeRosse, P., Ikuta, T., Peters, B. D., Karlsgodt, K. H., Szeszko, P. R., & Malhotra, A. K. (2014). Adding insult to injury: childhood and adolescent risk factors for psychosis predict lower fractional anisotropy in the superior longitudinal fasciculus in healthy adults. *Psychiatry Research*, *224*(3), 296–302. http://dx.doi.org/10.1016/j.pscychresns.2014.09.001.

Engelter, S. T., Provenzale, J. M., Petrella, J. R., DeLong, D. M., & MacFall, J. R. (2000). The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. *AJR American Journal of Roentgenology*, *175*(2), 425–430. http://dx.doi.org/10.2214/ajr.175.2.1750425.

Epstein, K. A., Cullen, K. R., Mueller, B. A., Robinson, P., Lee, S., & Kumra, S. (2014). White matter abnormalities and cognitive impairment in early-onset schizophrenia-spectrum disorders. *Journal of the American Academy of Child Adolescent Psychiatry*, *53*(3), 362–372. e361–e362. http://dx.doi.org/10.1016/j.jaac.2013.12.007.

Fitzsimmons, J., Kubicki, M., & Shenton, M. E. (2013). Review of functional and anatomical brain connectivity findings in schizophrenia. *Current Opinion in Psychiatry*, *26*(2), 172–187. http://dx.doi.org/10.1097/YCO.0b013e32835d9e6a.

Gilman, J. M., Kuster, J. K., Lee, S., Lee, M. J., Kim, B. W., Makris, N., … Breiter, H. C. (2014). Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *The Journal of Neuroscience*, *34*(16), 5529–5538. http://dx.doi.org/10.1523/jneurosci.4745-13.2014.

Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gonenc, A., & Lukas, S. E. (2014). Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology (Berlin)*, *231*(8), 1455–1465. http://dx.doi.org/10.1007/s00213-013-3326-z.

Haller, S., Curtis, L., Badan, M., Bessero, S., Albom, M., Chantraine, F., … Merlo, M. (2013). Combined grey matter VBM and white matter TBSS analysis in young first episode psychosis patients with and without cannabis consumption. *Brain Topography*, *26*(4), 641–647. http://dx.doi.org/10.1007/s10548-013-0288-8.

Ho, B. C., Andreasen, N. C., Nopoulos, P., Arndt, S., Magnotta, V., & Flaum, M. (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Archives of General Psychiatry*, *60*(6), 585–594. http://dx.doi.org/10.1001/archpsyc.60.6.58560/6/585.

Jacobus, J., McQueeny, T., Bava, S., Schweinsburg, B. C., Frank, L. R., Yang, T. T., & Tapert, S. F. (2009). White matter integrity in adolescents with histories of marijuana use and binge drinking. *Neurotoxicology and Teratology*, *31*(6), 349–355. http://dx.doi.org/10.1016/j.ntt.2009.07.006.

Jacobus, J., Squeglia, L. M., Infante, M. A., Bava, S., & Tapert, S. F. (2013). White matter integrity pre- and post marijuana and alcohol initiation in adolescence. *Brain Sciences*, *3*(1), 396–414. http://dx.doi.org/10.3390/brainsci3010396.

James, A., Hough, M., James, S., Winmill, L., Burge, L., Nijhawan, S., … Zarei, M. (2011). Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS). *Schizophrenia Research*, *128*(1–3), 91–97. http://dx.doi.org/10.1016/j.schres.2011.02.014.

Kim, D. J., Skosnik, P. D., Cheng, H., Pruce, B. J., Brumbaugh, M. S., Vollmer, J. M., … Newman, S. D. (2011). Structural network topology revealed by white matter tractography in cannabis users: a graph theoretical analysis. *Brain Connection*, *1*(6), 473–483. http://dx.doi.org/10.1089/brain.2011.0053.

Kubicki, M., & Shenton, M. E. (2014). Diffusion tensor imaging findings and their implications in schizophrenia. *Current Opinion in Psychiatry*, *27*(3), 179–184. http://dx.doi.org/10.1097/yco.0000000000000053.

Lebel, C., Caverhill-Godkewitsch, S., & Beaulieu, C. (2010). Age-related regional variations of the corpus callosum identified by diffusion tensor tractography. *NeuroImage*, *52*(1), 20–31. http://dx.doi.org/10.1016/j.neuroimage.2010.03.072.

Lim, K. O., Choi, S. J., Pomara, N., Wolkin, A., & Rotrosen, J. P. (2002). Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. *Biological Psychiatry*, *51*(11), 890–895.

McPartland, J. M., Glass, M., & Pertwee, R. G. (2007). Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. *British Journal of Pharmacology*, *152*(5), 583–593. http://dx.doi.org/10.1038/sj.bjp.0707399.

McPartland, J. M., Matias, I., Di Marzo, V., & Glass, M. (2006). Evolutionary origins of the endocannabinoid system. *Gene*, *370*, 64–74. http://dx.doi.org/10.1016/j.gene.2005.11.004.

Ozcelik-Eroglu, E., Ertugrul, A., Oguz, K. K., Has, A. C., Karahan, S., & Yazici, M. K. (2014). Effect of clozapine on white matter integrity in patients with schizophrenia: a diffusion tensor imaging study. *Psychiatry Research*, *223*(3), 226–235. http://dx.doi.org/10.1016/j.pscychresns.2014.06.001.

Peters, B. D., de Haan, L., Vlieger, E. J., Majoie, C. B., den Heeten, G. J., & Linszen, D. H. (2009). Recent-onset schizophrenia and adolescent cannabis use: MRI evidence for structural hyperconnectivity? *Psychopharmacology Bulletin*, *42*(2), 75–88.

Regenold, W. T., Phatak, P., Marano, C. M., Gearhart, L., Viens, C. H., & Hisley, K. C. (2007). Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. *Psychiatry Research*, *151*(3), 179–188. http://dx.doi.org/10.1016/j.psychres.2006.12.019.

Torii, Y., Iritani, S., Sekiguchi, H., Habuchi, C., Hagikura, M., Arai, T., … Ozaki, N. (2012). Effects of aging on the morphologies of Heschl's gyrus and the superior temporal gyrus in schizophrenia: a postmortem study. *Schizophrenia Research*, *134*(2–3), 137–142. http://dx.doi.org/10.1016/j.schres.2011.10.024.

Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., Goldberg, J., … Eaves, L. (1998). Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry*, *55*(11), 967–972.

Uranova, N. A., Vikhreva, O. V., Rachmanova, V. I., & Orlovskaya, D. D. (2011). Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: a postmortem morphometric study. *Schizophrenia Research Treatment*, *2011*, 325789. http://dx.doi.org/10.1155/2011/325789.

Villares, J. (2007). Chronic use of marijuana decreases cannabinoid receptor binding and mRNA expression in the human brain. *Neuroscience*, *145*(1), 323–334. http://dx.doi.org/10.1016/j.neuroscience.2006.11.012.

Williams, M. R., Galvin, K., O'Sullivan, B., MacDonald, C. D., Ching, E. W., Turkheimer, F., … Maier, M. (2014). Neuropathological changes in the substantia nigra in schizophrenia but not depression. *European Archives of Psychiatry and Clinical Neuroscience*, *264*(4), 285–296. http://dx.doi.org/10.1007/s00406-013-0479-z.

Yucel, M., Zalesky, A., Takagi, M. J., Bora, E., Fornito, A., Ditchfield, M., … Lubman, D. I. (2010). White-matter abnormalities in adolescents with long-term inhalant and cannabis use: a diffusion magnetic resonance imaging study. *Journal of Psychiatry and Neuroscience*, *35*(6), 409–412. http://dx.doi.org/10.1503/jpn.090177.

Zalesky, A., Solowij, N., Yucel, M., Lubman, D. I., Takagi, M., Harding, I. H., … Seal, M. (2012). Effect of long-term cannabis use on axonal fibre connectivity. *Brain*, *135*(Pt 7), 2245–2255. http://dx.doi.org/10.1093/brain/aws136.

Zhang, R., Wei, Q., Kang, Z., Zalesky, A., Li, M., Xu, Y., … Huang, R. (2014). Disrupted brain anatomical connectivity in medication-naive patients with first-episode schizophrenia. *Brain Structure and Function*, *220*(2), 1145–1159. http://dx.doi.org/10.1007/s00429-014-0706-z.

Zhu, J., Zhuo, C., Qin, W., Wang, D., Ma, X., Zhou, Y., & Yu, C. (2015). Performances of diffusion kurtosis imaging and diffusion tensor imaging in detecting white matter abnormality in schizophrenia. *NeuroImage: Clinical*, *7*, 170–176. http://dx.doi.org/10.1016/j.nicl.2014.12.008.